REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

In response to the Final Office Action mailed April 10, 2009, and the Advisory Action of July 15, 2009, Claims 1-6 stand pending. Claims 1, 3 and 5 are amended. Support for the amendments to the claims may be found generally throughout the specification and more specifically within pages 2-4 and 7 of the specification. No new matter has been added.

It is submitted that these claims, as originally presented, were in full compliance with the requirements of 35 U.S.C. §112. Further, the amendments and remarks presented herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §101, §102, §103, or §112. Rather, the amendments and remarks are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Claim Rejections – 35 USC § 112

Claims 1-6 are rejected under 35 USC 112, 1st paragraph, for alleged lack of enablement. The Examiner contends that Claims 1 and 5 do not provide enablement for any subfragment of SEQ ID NOs:3 and 2 respectively. The Examiner does acknowledge enablement for nucleic acids and methods of producing HGF fragments comprising at least amino acids 32-207. Applicants traverse and overcome this rejection.

Although Applicants disagree with the Examiner's rationale, the amendment to claims 1, 3 and 5 obviates the rejection. Consequently, reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 USC § 103

Claims 1-6 remain rejected under 35 USC 103(a) as being unpatentable over Stahl et al in view of three additional references Fuglsang, Olivares-Trejo et al, and Jeh et al for reasons of record. Applicants respectfully traverse and overcome this rejection as set forth below, first with regard to Claims 1-4 and second with regard to Claims 5-6.

1) First, Applicants respectfully note that the asserted combination of references do not anticipate, nor render obvious, all elements of Claim 1 or 3 or dependent claims thereon.[1] Claims 1 and 3 require, in part, that the amino acid at position 1 of SEQ ID NO:3 is methionine and the amino acid at position 2 is serine. Stahl does not teach, nor suggest, such requirements. Similarly, Fuglsang, Olivares-Trejo et al, and Jeh et al, also do not teach, nor suggest such requirements.

Applicants therefore respectfully submit that the cited art therefore does not teach nor suggest Claims 1 and 3. Accordingly, Applicants respectfully request that the 103(a) rejection be withdrawn and that said claims, and dependent claims thereon, be placed into condition for allowance.

2) Second, with regard to claims 5-6, the Examiner contends that basically Stahl discloses recombinant human hepatocyte growth factor isoforms produced in E. coli, but acknowledges Stahl's failure to disclose substitution of a CGT codon at positions 33, 35 and 36 of NK1/NK2. The Examiner alleges that Fuglsang discloses CGT as the most optimal codon for Arg, that Olivares-Trejo discloses increase of <u>a different protein</u> in E.coli when arginine codons AGA and AGG in said <u>different protein</u> are changed to CGT and that finally Jeh discloses that in the production of <u>yet another different protein</u>

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[1] Claims 1-4 are directed to SEQ ID NO: 3, wherein said sequence contains as first encoded amino acid a methione, which is <u>not</u> part of the amino acid sequence of HGF. There is <u>no</u> indication, <u>no</u> teaching and <u>no</u> suggestion in any of the cited references, singularly or taken together, of using or encoding SEQ ID NO: 3. Accordingly, Applicants respectfully submit that the cited references citing different sequences and/or completely different proteins do <u>not</u> render Applicants claimed invention regarding SEQ ID NO:3 obvious.

(fGH) in E.coli, that changing the first 15 codons of fGH with other codons, including CGT for Arg, resulted in better production of this <u>yet another different protein.</u> Applicants respectfully traverse and overcome this rationale for the reasons set forth below.

a) First, Applicants respectfully point out that the Examiner at best has only shown results involving <u>different</u> proteins. Olivares-Trejo is directed to the expression of the int gene and is completely silent about HGF. Jeh is also directed to the expression of a different protein and involves many different and multiple simultaneous codon changes as being related to better expression. Applicants respectfully submit that neither Olivares-Trejo nor Jeh are relevant art to the instant application.

b) Second, Applicants respectfully submit that the cited references actually do not teach nor disclose the Examiner's suggested interpretation. For example, Fuglsang et al is directed to "the effective number of codons for individual amino acids". The codon usage of Arg is <u>not</u> discussed in this document. Only in Table 2 on page 188 the correlation between the RSCU value and the Nc(AA) or CAI value, respectively is given. Further it is outlined on page 187, right column, end of the column, that "Table:2 list the correlation coefficient for all codons belonging to the amino acids under investigation in this study, and it can be seen that when a significant and negative correlation is observed, then the codon is optimal, <u>but</u> an optimal codon does <u>not necessarily</u> show negative correlation" (emphasis added). On page 189, left column, it is outlined that "that optimality is not a phenomenon that is confined solely to expressivity, but that <u>other factors</u> might render a codon optimal under certain conditions" (emphasis added). Additionally, the complete document is <u>silent about the optimal codon for the amino acid Arg</u>, and in table 2 <u>two</u> codons are listed which may be used as optimal codons (emphasis added).

Thus, Fuglsang et al does <u>not</u> provide a hint towards an optimal codon for the amino acid Arg and, furthermore, it qualifies its own findings by admitting, that other factors beside the codon may render a codon optimal. Therefore, a person skilled in the

art would not take the teach of Fuglsang et al as to favor a specific codon but only that there may exist a codon that is preferred in comparison to their codons.

Moreover, as noted above, Olivares-Trejo et al is directed to the expression of the int gene. Most importantly, Olivares-Trejo et al is completely silent about HGF and is also completely silent about high yield production. Further, Olivares-Trejo et al reports that "cell growth and int protein synthesis were enhanced by overexpression of Pth and tRNA^{Arg4} cognate to AGG and AGA but not of tRNA^{Ile2a} specific for ATA. The increase of int protein synthesis also takes place when the rate arginine codons AGA and AGG at positions 3 and 4 are changed to common arginine CG% or lysine AAA codons but not to rate isoleucine ATA codons".

Thus, Olivares-Trejo et al provides for at least three alternatives, i.e. expression of the tRNA required for the codon or change of the codons to codons encoding the same amino acid or change of the codons to codons encoding lysine. Furthermore, this has only been exemplified for the int protein. Therefore, a person skilled in the art would not be motivated to take the teaching of Olivares-Trejo et al into account when looking for a method related to a completely different protein, HGF, much less SEQ ID NO:3.

Accordingly, Applicants submit that a combination of Stahl et al, Fuslang and Oliveras-Trejo et al would not result in the current invention.

Finally, as noted, Jet et al is directed to "recombination flounder growth hormone form Escherichia coli". The first 15 codons have been randomly mutagenized. As a result two genes encoding fGH have been identified. When compared to the original codon sequence it can be clearly seen that more than one codon is changed and that changes to optimal as well as rare codons occurred (emphasis added, fig. 3, page 187).

Thus, a person skilled in the art can conclude from the teaching of Jeh et al that for codon optimization i) more than one change of a codon is required and ii) that not

only changes to optimal codons are required but also changes to rare codons are required, i.e. <u>a balance between changes to both optimal and rare codons must exist</u>. Applicants respectfully submit that the teaching of Jeh requires a balance of such changes to codons and as such, one cannot cherry-pick codons (from other references, dealing with different proteins) without taking the requirement for balance into account. Therefore, a combination of Stahl et al, Fsulang, Oliveras-Trejo and Jeh et al would <u>not</u> result in the current invention.

Accordingly, Applicants respectfully request that the 103(a) rejection be withdrawn and that Claims 5-6 as herein presented be also placed into condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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